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A HETERO PAUSON–KHAND REACTION OF KETENIMINES: A NEW SYNTHETIC METHOD FOR γ -EXOMETHYLENE- α , β -UNSATURATED γ -LACTAMS[†]

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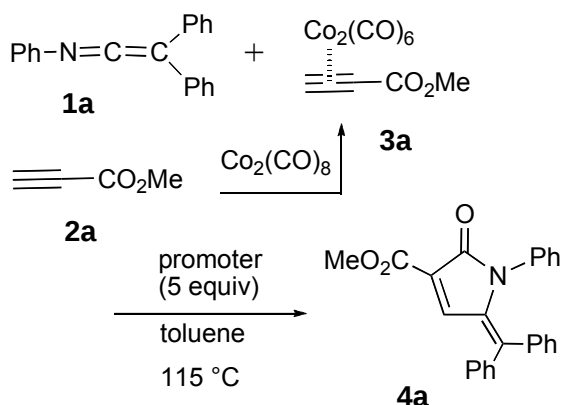
Abstract – A novel ketenimine Pauson–Khand reaction has been described for the first time. *C,C,N*-Triarylketenimines reacted with alkyne–dicobalthexacarbonyl complexes upon heating in toluene in the presence of dimethyl sulfoxide as a promoter to afford γ -lactams, 5-(diphenylmethylene)-1*H*-pyrrol-2(5*H*)-ones, in good yields.

The Pauson–Khand reaction, formally a cobalt-mediated three-component [2 + 2 + 1] cocyclization of an alkyne, an alkene and carbon monoxide, constitutes one of the most useful, convergent and atom-economical methods for the synthesis of a cyclopentenone.^{1–4} Since the first publications in the early 70s,¹ many advances in this method and its related processes have been made, involving discovery or improvement of promoters to effect the reaction, the Pauson–Khand type reaction mediated by other metals, the allenic or electron-deficient alkenic Pauson–Khand type reaction, and the catalytic variant as well as the asymmetric version.^{2–4} A hetero Pauson–Khand type reaction has also been developed in which a hetero-alkene π -component such as a carbonyl (ketone and aldehyde) or an imine is used instead of an alkene or alkyne partner to give a γ -butyrolactone⁵ or a γ -butyrolactam.⁶ Recently, a heterocumulenic Pauson–Khand type reaction was reported from our laboratory in which alkyne-carbodiimides were used as an alkyne-hetero-alkene partner to give [2 + 2 + 1] cyclocarbonylation products, pyrrolo- or indolo-fused γ -lactams.^{7–9} Mukai et al. applied a catalytic version of this carbodiimide Pauson–Khand reaction for synthesis of hexahydropyrrolo[2,3-*b*]indole alkaloids.¹⁰ The

[†] This paper is dedicated to Professor Dr. Akira Suzuki on occasion of his 80th birthday.

synthetic utility of such heterocumulenic Pauson–Khand type cyclocarbonylation has also been enhanced by the synthesis of poly-substituted maleimides, in which the reaction involved the ruthenium-catalyzed intermolecular $[2 + 2 + 1]$ cocyclization of isocyanates, alkynes, and carbon monoxide.¹¹ Alkyne-isothiocyanates have also been used successfully in the heterocumulenic Pauson–Khand type method leading to indolo- γ -thiolactones (thieno[2,3-*b*]indol-2-ones).¹² A ketenimine is now our target molecule for evaluating the heterocumulene-mediated $[2 + 2 + 1]$ cocyclization reaction. We herein report the first example of the ketenimine Pauson–Khand reaction.

We took a fundamental protocol using $\text{Co}_2(\text{CO})_8$ for the intermolecular Pauson–Khand reaction among a ketenimine (**1**),¹³ an alkyne (**2**), and CO. In a model reaction between ketenimine **1a** and the preformed methyl propiolate- $\text{Co}_2(\text{CO})_6$ complex **3a** (Scheme 1), the desired ketenimine Pauson–Khand reaction did not proceed in the absence of a promoter even after refluxing in toluene for 8 h (Table 1, entry 1). Therefore, in order to find an efficient promoter for accelerating the ketenimine Pauson–Khand reaction, the reactions in the presence of promoters such as $\text{P}(\text{OPh})_3$, *N*-methylmorpholine oxide (NMO), $(\text{CH}_2)_5\text{S}$, CH_3CN , dimethylformamide (DMF), and dimethyl sulfoxide (DMSO) were examined (entries 2-7). Among the promoters tested, DMSO^{3,14} was found to most effectively accelerate the Pauson–Khand reaction for producing 5-(diphenylmethylene)-2-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate methyl ester (**4a**)^{15,16} in a fair yield (50%, entry 7).



Scheme 1. Efficiency of promoters in a model P-K reaction between **1a** and **3a**.

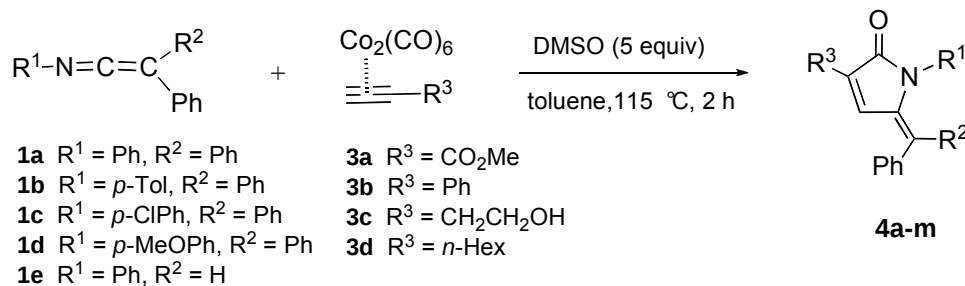
Table 1. Screening of promoters

Entry	Promoter	Time / h	Yield of 4a / %
1	none	8	0
2	$\text{P}(\text{OPh})_3$	8	0
3 ^{a)}	NMO	4	trace
4	$(\text{CH}_2)_5\text{S}$	2	11
5	MeCN	2	19
6	DMF	2	25
7	DMSO	2	50

a) In the presence of MS4A.

With the optimal promoter (DMSO) and conditions identified, the scope of the reaction with respect to both substrates, ketenimine (**1**) and alkyne-complex (**3**), bearing a variety of substituents (R^1 , R^2 , and R^3) was then examined (Scheme 2). The results are shown in Table 2. Thermally stable *C,C,N*-triarylketenimines **1a-d** were found to be good components in the Pauson–Khand reaction with the cobalt-alkyne complex **3a-d** having a variety of substituents to give the desired γ -methylene- γ -lactams **4a-m** in moderate to good yields (entries 1-13). In contrast, the reaction of ketenimine **1e** ($\text{R}^2 = \text{H}$) with

3a failed, and the product **4n** was not detected (entry 14). This is probably due to the thermal instability of ketenimine **1e** and its cobalt complex, which readily isomerize and/or polymerize under the employed conditions.¹³



Scheme 2. Scope of the ketenimine Pauson–Khand reaction to give γ -lactams **4**.

Table 2. Scope of the ketenimine Pauson–Khand reaction to give γ -lactams **4** bearing a variety of substituents.

Entry	Ketenimine	Alkyne-complex	R^1	R^2	R^3	Product	Yield / %
1	1a	3a	Ph	Ph	CO_2Me	4a	50
2	1b	3a	<i>p</i> -Tol	Ph	CO_2Me	4b	45
3	1c	3a	<i>p</i> -ClPh	Ph	CO_2Me	4c	43
4	1a	3b	Ph	Ph	Ph	4d	69
5	1b	3b	<i>p</i> -Tol	Ph	Ph	4e	45
6	1c	3b	<i>p</i> -ClPh	Ph	Ph	4f	46
7	1d	3b	<i>p</i> -MeOPh	Ph	Ph	4g	77
8	1a	3c	Ph	Ph	$\text{CH}_2\text{CH}_2\text{OH}$	4h	50
9	1b	3c	<i>p</i> -Tol	Ph	$\text{CH}_2\text{CH}_2\text{OH}$	4i	46
10	1c	3c	<i>p</i> -ClPh	Ph	$\text{CH}_2\text{CH}_2\text{OH}$	4j	53
11	1a	3d	Ph	Ph	<i>n</i> -Hex	4k	53
12	1b	3d	<i>p</i> -Tol	Ph	<i>n</i> -Hex	4l	47
13	1c	3d	<i>p</i> -ClPh	Ph	<i>n</i> -Hex	4m	43
14	1e	3a	Ph	H	CO_2Me	4n	0

In summary, the ketenimine Pauson–Khand reaction was realized yielding γ -methylene- γ -lactams, though usable ketenimines were limited to thermally tolerant triarylketenimines.

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examples of such heterocumulenic [2 + 2 + 1] cocyclization had been reported. These involved the intermolecular reaction of diphenylcarbodiimide or phenyl isocyanate with diphenylacetylene and Fe(CO)₅ or Ni(cod)₂, which indeed afforded a hetero Pauson–Khand type product: (a) Y. Ohshiro, K. Kinugasa, T. Minami, and T. Agawa, *J. Org. Chem.*, 1970, **35**, 2136; (b) H. Hoberg and B.W. Oster, *J. Organomet. Chem.*, 1982, **234**, C35.

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15. A mixture of the dicobaltoctacarbonyl (622 mg, 1.82 mmol) and methyl propiolate (**2a**, 153 mg, 1.82 mmol) in CH₂Cl₂ (10 mL) was stirred at room temperature for 2 hours. Removal of the solvent and column chromatography of the residue on silica gel (hexane/EtOAc (3:1)) afforded quantitatively the dicobalthexacarbonyl-methyl propiolate complex (**3a**) as an oil. A mixture of **3a** (112 mg, 0.303 mmol), *C,C,N*-triphenylketenimine (**1a**,¹³ 97.8 mg, 0.363 mmol) and DMSO (0.11 mL, 1.52 mmol) in toluene (5 mL) was heated at 115 °C for 2 hours. The reaction mixture was evaporated and the residue was chromatographed on silica gel, eluting with hexane/ EtOAc (3:1), to give the P–K product **4a** (57.8 mg, 50%).
16. Methyl 5-(diphenylmethylene)-2-oxo-1-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**4a**): Yellow solid, mp 149.0–151.0 °C; ¹H-NMR (300 MHz, CDCl₃) δ : 7.82 (s, 1H), 7.24–7.47 (m, 5H), 6.83–7.01 (m, 10H), 3.89 (s, 3H); ¹³C-NMR (76 MHz, CDCl₃) δ : 166.8 (CO), 162.7 (CO), 146.4 (CH), 140.0 (C), 137.5 (C), 137.0 (C), 135.8 (C), 135.3 (C), 132.0 (2CH), 131.1 (2CH), 129.5 (CH), 128.7 (CH), 128.4 (2CH), 128.0 (2CH), 127.3 (2CH), 127.0 (2CH), 126.3 (CH), 122.6 (C), 52.2 (CH₃).; IR (KBr): 1754, 1686, 1560, 1346, 1190, 1064, 740, 688 cm⁻¹. HRMS-ESI (*m/z*): Calcd for C₂₅H₁₉NO₃: [M]⁺ 381.1365. Found: 381.1358.
17. The structure **4** was determined spectroscopically (IR, ¹H- and ¹³C-NMR). Particularly, the observed prominent ¹³C-NMR chemical shift values are in good agreement with those calculated for the structure **4** rather than those for the other possible chemo- and regio-isomers. The structure **4** was further supported by the fact that in the HMBC measurement, the correlation between the olefinic proton and the carbons (³J_{H-C}, enamino β-carbon, two carbonyl carbons) was observed.